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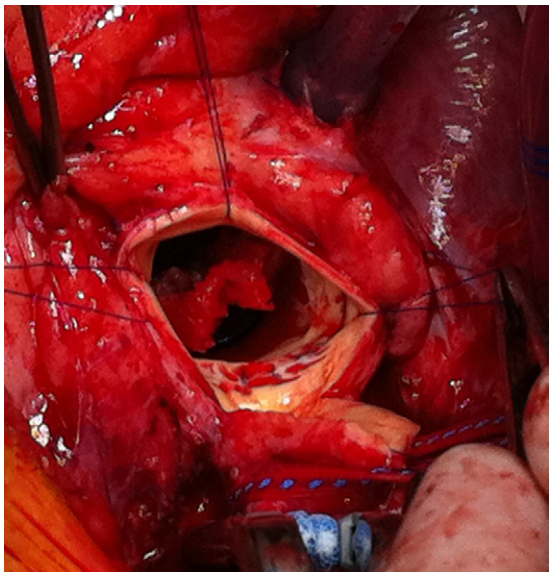

Figure 2 Thrombosed Aortic Valve Prosthesis

Surgical photograph demonstrating the intraoperative appearance of the prosthetic aortic valve. Significant thrombus was observed on both the ventricular and aortic sides of the prosthesis.

A mitral valve replacement and tricuspid valve repair were performed. The patient had an uneventful recovery.

Discussion. Thrombosis of a mechanical valve is a potentially fatal complication. With warfarin anticoagulation, the incidence of valve thrombosis is low (1). In both presented cases, patients were anticoagulated with warfarin and had never experienced thrombotic or bleeding events. One month after being switched from warfarin to dabigatran both patients became symptomatic and were subsequently diagnosed with thrombosis. While a causal link is not certain, the temporal association is highly suggestive.

Dabigatran is one of several novel oral anticoagulants evaluated as a substitute for warfarin. Regulatory approval was based on the pivotal RE-L-Y (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, which compared dabigatran to warfarin for the treatment of nonvalvular AF (2). This study demonstrated equivalent freedom from thrombotic events with fewer hemorrhagic events for low-dose dabigatran (110 mg, twice daily) and superior freedom from thrombotic events with equivalent bleeding with higher dose dabigatran (150 mg, twice daily). Additional advantages of dabigatran include stable dosing, no requirement for monitoring, and fewer interactions.

In vitro and animal studies suggest that Dabigatran for mechanical valve anticoagulation may be a potential therapeutic avenue (3,4). Recently, enoxaparin was compared to dabigatran for anticoagulation of mechanical aortic valves. Dabigatran was found to reduce thrombus burden with a dose of 20 mg/kg twice daily, corresponding to an aPTT of 2 to 2.5 times normal in the porcine model. This question is now being addressed with a phase II clinical trial, RE-ALIGN (NCT01452347), which utilizes doses ranging from 150 to 330 mg twice daily, adjusted based on renal function and results of the Hemoclot assay.

The failure of 1 patient to achieve adequate anticoagulation despite a "highdose" and that a second experienced valve thrombosis despite therapeutic aPTT levels highlights the importance of medication testing for a specific indication. Furthermore, AF may represent a lesser thrombotic risk than a mechanical prosthesis, particularly mitral. While there is a wealth of data and clinical experience on dosing and therapeutic response to warfarin in this context, these data are unavailable for dabigatran.

Off-label use of novel drugs can jeopardize potential future applications in new disease contexts and should be avoided until data from well-designed clinical studies is available. Novel oral anticoagulants hold tremendous promise for mechanical valve anticoagulation. However, there is a need for dose-finding studies and clinical trials to demonstrate safety and efficacy in this setting.

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Letters to the Editor

^{18}F-Fluoride Imaging for Atherosclerosis

We read with great interest the article on coronary artery calcification by Dweck et al. (1) recently published in the *Journal*. Although the authors claimed that this communication was the first on this topic in the literature, we would direct the readership to our original article, "Detection and global quantification of cardiovascular molecular calcification by fluoro18-fluoride positron emission tomography/computed tomography—a novel concept" (2) and accompanying editorial, "Assessing global cardiovascular

molecular calcification with ^{18}F-fluoride PET/CT: will this become a clinical reality and a challenge to CT calcification scoring?" (3), published earlier on the same topic.

In addition, we take issue with a number of points made by the authors (1). Although we agree with them that it is feasible to detect cardiac calcifications using ^{18}F–sodium fluoride far in advance of visualizing this phenomenon with x-ray computed tomography (CT), attempts to image coronary artery calcification by visualizing the artery on CT scan are challenging for a variety of reasons. First, it is extremely difficult to localize the coronary arteries without the assistance of contrast dye. The administration of x-ray contrast agent is not practical for screening of individuals at risk, given the potential toxicity of these agents. As noted by the investigators (1), it is necessary to assign regions of interest on clearly visualized calcifications on CT scan for detecting the ongoing calcification. Because the power of ^{18}F–sodium fluoride technology lies in its early ability to detect molecular calcification in advance of structural abnormalities observed on CT scan, assigning a region of interest based on coronary artery calcification is not feasible in early disease in younger patients. Second, the authors (1) failed to address the need for partial volume correction, which is of importance in such small structures as coronary arteries because loss of signal or spillover from adjacent signal may occur when a relatively small region of interest is evaluated. Particularly, motion artifacts due to the cardiac cycle further degrades the spatial resolution and necessitates partial volume correction. Third, the blood pool correction for background activity of tracer adds further complexity and potential error.

We believe that a methodology independent of recognition of vascular distribution, a global assessment, will be of great value in detecting early disease before calcification is apparent on electron beam CT imaging. The methodology that we presented in publications predating the recent article by Dweck et al. (1) describes a global assessment of molecular calcification detected with ^{18}F–sodium fluoride. Although the methodology described in this article (1) appears to be reproducible by the investigators involved, this may not be the case for inexperienced practitioners. A global assessment of cardiac calcification obviates the need for partial volume correction and therefore is essential in assessing overall calcification in the heart. In addition, a global approach allows for delayed imaging of 2 to 3 h after the administration of sodium fluoride, which would obviate the need for blood pool correction.

There is certainly a dire need for visualizing atherosclerotic disease in early stages and ^{18}F–sodium fluoride imaging may realize this objective. Prospective, randomized clinical trials are needed to determine the feasibility and clinical benefit of ^{18}F–sodium fluoride imaging for early atherosclerotic disease.

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Reply

We thank Dr. Mohler and colleagues for their interest in our study and for their communication. We agree that prospective randomized clinical trials are now required to assess the clinical benefit of cardiovascular ^{18}F–sodium fluoride (^{18}F-NaF) scanning.

Our paper was the first prospective description of ^{18}F-NaF uptake in the coronary arteries of patients specifically studied to assess the heart (1). The highlighted paper by Behshti et al. (2) described ^{18}F-NaF activity within the heart in a small retrospective cohort of patients with cancer that did not localize ^{18}F-NaF uptake to the coronary arteries. Their approach was to draw ellipsoid regions of interest around the cardiac silhouette on noncontrast axial images. We previously demonstrated that ^{18}F-NaF activity also occurs within noncoronary structures in the heart, most notably the aortic valve and mitral valve annulus (1). As such, cardiac and coronary ^{18}F-NaF uptake cannot be considered synonymous.

There is the further question of whether it is possible to measure ^{18}F-NaF uptake only in the coronary vessels. We demonstrated that this is the case and is evidenced in the images and the excellent measures of reproducibility we obtained and reported in our paper. Most of our population with aortic stenosis had high calcium scores, and so it was readily possible to determine the course of the coronary arteries on both the electrocardiogram-gated and nongated scans. We accept that in patients with less advanced disease, computed tomography coronary angiography will be required to better visualize the lesions displaying increased ^{18}F-NaF uptake. Indeed we are currently conducting such a study and can localize ^{18}F-NaF uptake not only to individual coronary arteries but also individual plaques and their components.

We recognize that the issue of partial volume averaging is important in positron emission tomography (PET) imaging. However, the spatial resolution of PET is approximately 3 mm. We are interested in localizing ^{18}F-NaF activity to individual plaques, which are commonly 20 to 30 mm long in vessels with a diameter of 3 to 4 mm. Therefore, our approach is well within the spatial resolution of PET, especially given the very high signal-to-background ratio observed with ^{18}F-NaF in the heart. Quantifying the maximum uptake value is straightforward as reflected by our excellent measures of reproducibility, and we are confident that our approach will be reproduced by other groups. Indeed, several studies have confirmed the feasibility of this approach using ^{18}F-fluorodeoxyglucose in the coronary arteries (2,3).

Given the above, we do not believe that a volume of interest approach to the measurement of ^{18}F-NaF uptake in the heart is warranted. This would result in coronary arterial ^{18}F-NaF measures being conflated with valvular uptake. In addition, that approach would fail to harness the high sensitivity and spatial